Medicinal Chemistry
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Tutorial 08
Determination of Drug-Receptor Interactions, Conformation of Cyclic and Acyclic Structures etc.

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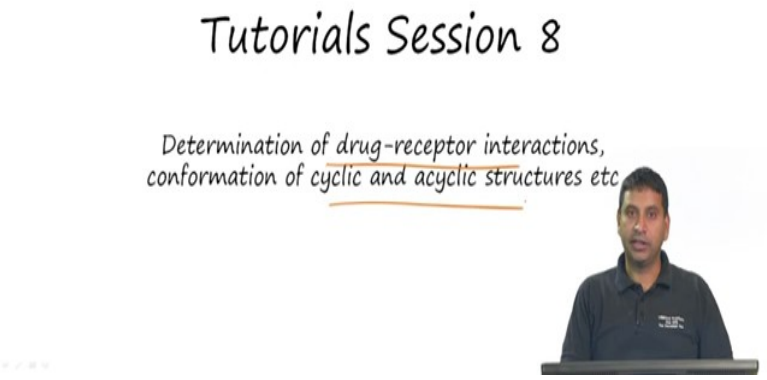

Welcome to the tutorial session, so today is session we are going to look at some problems which are discussing concepts on drug receptor interactions and also we look at some stereo chemical issues see the conformation of cyclic and acyclic structures.

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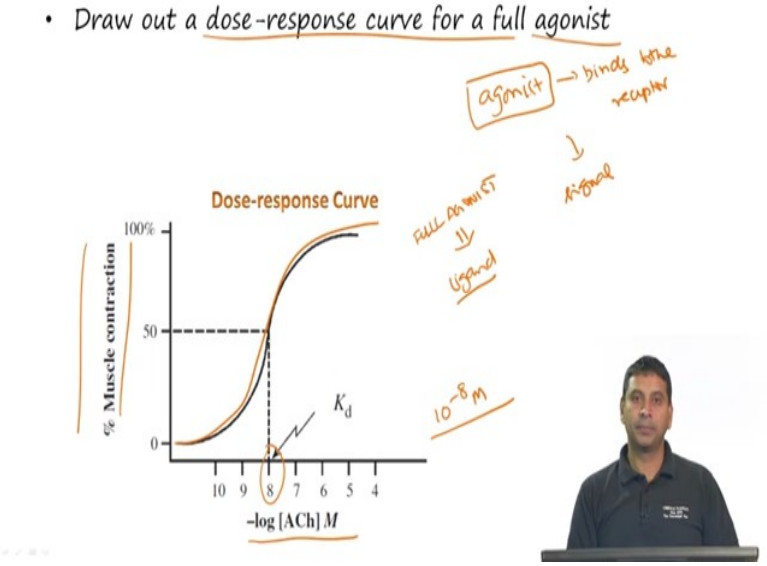

So to begin with let us look at some drug receptor interactions, so the first question is draw out a dose response curve for a full agonist, so we have already studied or we have already

looked that agonist is basically a compound that binds to the receptor and it also generates a signal much like the natural ligand does, so an agonist is an essentially close to or very similar to the natural ligand, so here is a Dose response curve for the natural ligand and so what we looking at on the Y axis is the % Muscle contraction and the X axis is the concentration.

So we already seen this in class and so the dissociation constant K_d is shown here which is basically 10 power minus 8, right molar. Now the question here is draw out the dose response curve for a full agonist, ok. So here what we mean by the word full agonist is that it binds or it carries out the function identical to the natural ligand, so a full agonist would be essentially the same as the natural ligand, ok and so if the % Muscle contraction is elicited by binding of the natural ligand then for the full agonist we would have an identical curve, ok. So the dose response curve for a full agonist would be essentially identical to that of the natural ligand.

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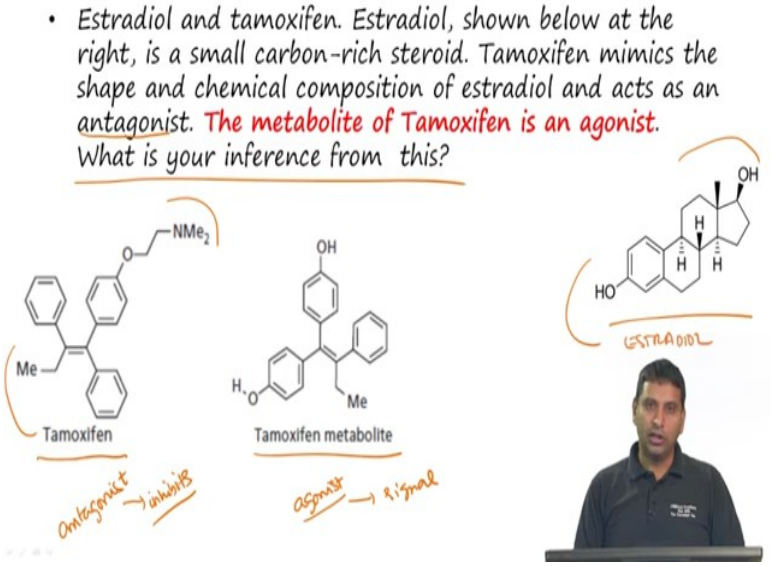

The next question is Estradiol and Tamoxifen. Estradiol which is shown here is a carbon rich steroid, ok and Tamoxifen which is a clinically used drug mimics the shape and chemical composition of Estradiol, ok so you see there are some similarities in the functional groups and it acts as antagonist so Tamoxifen is actually an antagonist lets write that down antagonist ok to Estradiol.

Now the metabolite of Tamoxifen that is shown here is an agonist, right so let us recall what antagonist or an agonist is? Antagonist inhibits the function of the receptor or reduces the signal transmission by the receptor by binding to the same site pretty much as the natural

ligand and agonist on the other hand competes for the same site but it increases or elicits the same response.

So the difference between the antagonist and agonist in this case is that one has not function which is exactly opposite to the other. So the question here is what is your inference from this? So to recap we a dealing with a commercially or clinically used drug Tamoxifen which is antagonist and it inhibits the binding of Estradiol and its metabolite which is shown here which is act as an agonist.

So the inference from this is that there must be some binding groups which is obviously binds to the Estradiol which binds similar over here, right and whatever the binding that happens with the Tamoxifen does not induced the conformational change required for the signal to be transmitted, ok. So in the case of Tamoxifen it binds to the receptor binding site but it does not induce the conformation change that is required for the signal to be transmitted but the metabolite tub of Tamoxifen binds to the same side and induces the same conformational change that Estradiol perhaps does and is able to act as a agonist.

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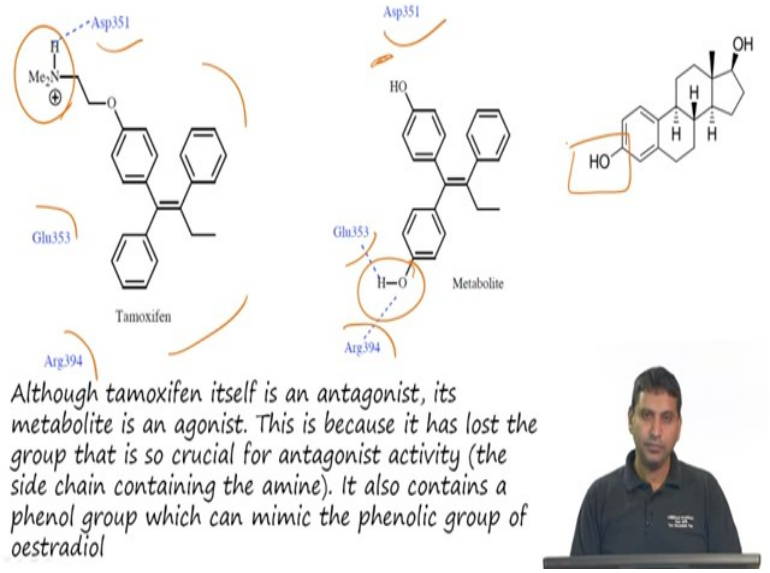

So this is the major inference from this data to look at it somewhat at a molecular level let us look at this picture over here it is known that these residues aspartate, glutamate and arginine are important in binding to the natural substrate and so what happens in the case of Tamoxifen is that these dimethylamino functional groups which is protonated binds to or weakly interacts with us parted and the rest of molecule mimics the shape and size of Estradiol, whereas the metabolite as you can see here has an extra hydroxyl group over here and this interaction is gone. So this extra hydroxyl group makes it much closer in structured

to Estradiol and perhaps this mimics the natural way of binding and it is starts becoming an agonist, ok.

So this is an example of how making of a compound which can act as a drug on its own but ones it get metabolised some part of it can actually function very differently in fact opposite to what you wanted to work on. So therefore understanding how drug under goes metabolism and what the byproducts are is an important and crucial part of drug discovery.

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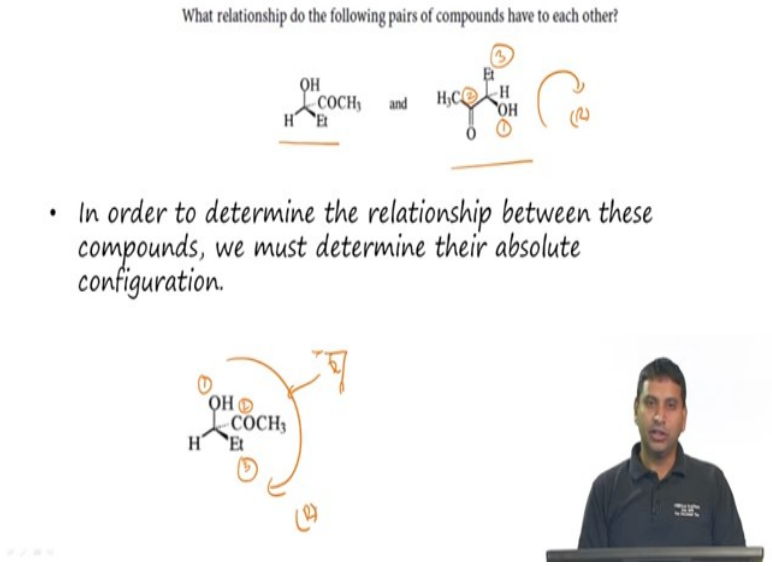

The next question will look at some stereochemistry? What is a relationship between this compound here and this compound here? So in order to do this let us first determine the absolute stereochemistry, so the absolute stereochemistry of these molecule we need to assign the priorities, so this would be priority no. 1, so this would be priority no. 2, so this would be priority no. 3, so hydrogen is behind us so these would be R, ok. So priority for this molecules similarly we can assign it based on OH 1, $COCH_3$ 2, Ethyl is 3 and so we need to look at it from here if you look at it from here 1, 2, 3 clockwise so these would also be R, ok.

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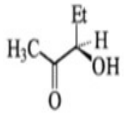

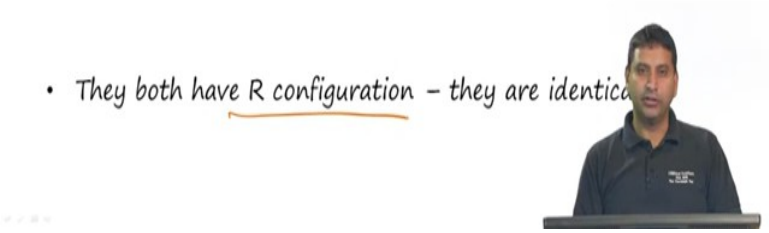

So these two molecules are identical they both have R Configuration.

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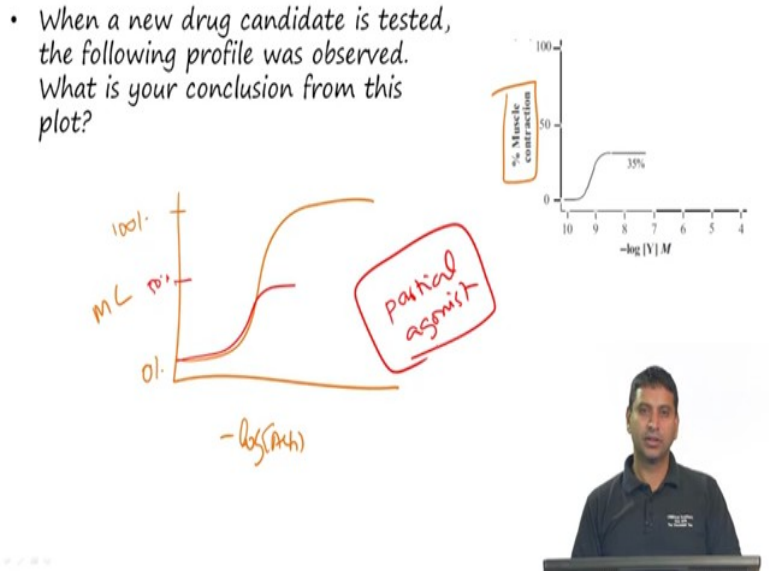

So in the next question will go back to our receptor binding, ligand binding. So when new drug candidate is tested the following profile is observed where you have % Muscle contraction to be 35%, so what is your conclusion from this? So in order to addressed this question we would assume that the natural ligand here which is acetylcholine has 100% Muscle contraction versus concentration and so if this the profile of the natural substrate the profile of the unnatural substrate looks something like this, right. So if this is 50% then it's less than 50% and so this would be a partial agonist, ok.

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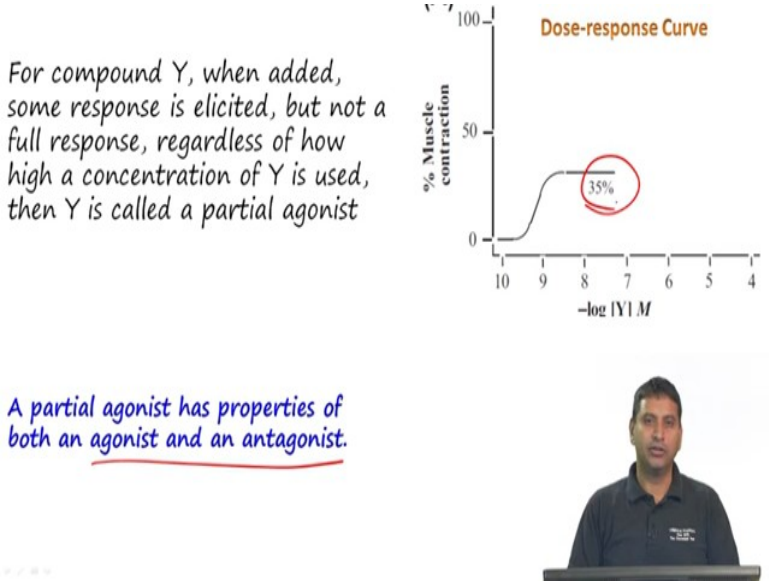

So the partial agonist has both the properties of an agonist as well as antagonist, ok. So if it is full agonist then we already looked that whatever conformational change that occurs with the natural ligand will also occur with the full agonist and you will see nice increase in the Muscle contraction but here since it acting both agonist as well as antagonist you do not see complete Muscle contraction in the Dose response curve. So therefore you call it a partial agonist, ok.

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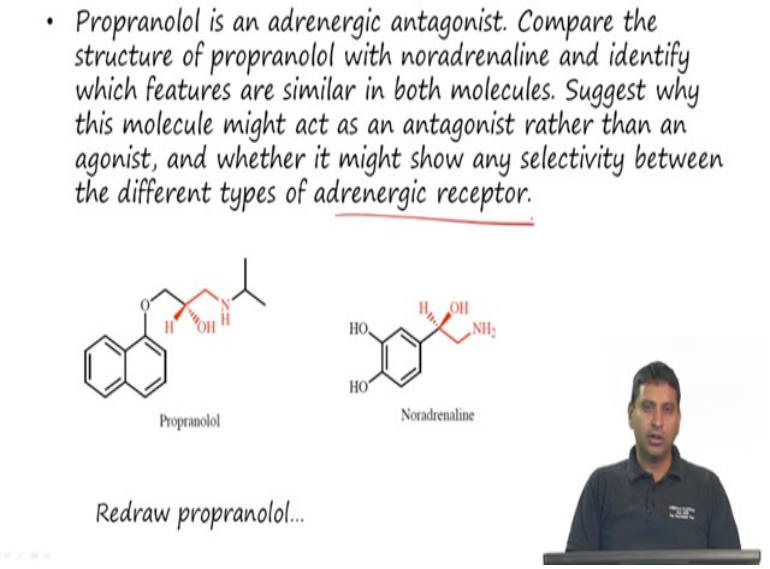

So the next question is Propranolol is an adrenergic antagonist, Compare the structure of Propranolol with noradrenaline and identify which features are similar in both molecules? Then suggest why these molecules might act as an antagonist rather than as agonist and whether it might show any selectivity between the different types of adrenergic receptors?

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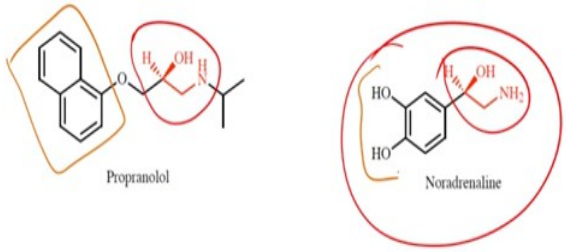

- Therefore, it is possible for this moiety in both molecules to form similar interactions with the receptor. However, the aromatic systems are different and so different interactions are possible here, which can account for propranolol acting as an antagonist rather than as an agonist if a different induced fit results

So in order to address this question first let us redraw Propranolol and if we redraw it and in a conformation that is very similar to noradrenaline we find that there are obviously very there are number of similarities in this so as shown here in red these is the so here is the active structure as shown here and what we have in addition is these extremely bulky naphthyl group which is going to be quite hydrophobic and there you don't have that kind of a group and you have these two hydroxyl groups which are going to have hydrogen bonding interaction perhaps, ok.

So therefore it is possible for these moiety in both molecules to form similar interactions with the receptors, ok. But because the aromatic systems are very different and so different that it is likely that it will acts as an antagonist rather as an agonist, ok because it is quite unlikely that the receptor will have the same induced fit from binding to noradrenaline or as well as Propranolol. So it is quite possible that this compound will act as an antagonist.

Now in order to understand whether it is going to have selectivity we would need to find out whether these molecules how these molecule varies across various isoforms of this receptor and that it may not be easy to predict beforehand whether it would have some selectivity or not.

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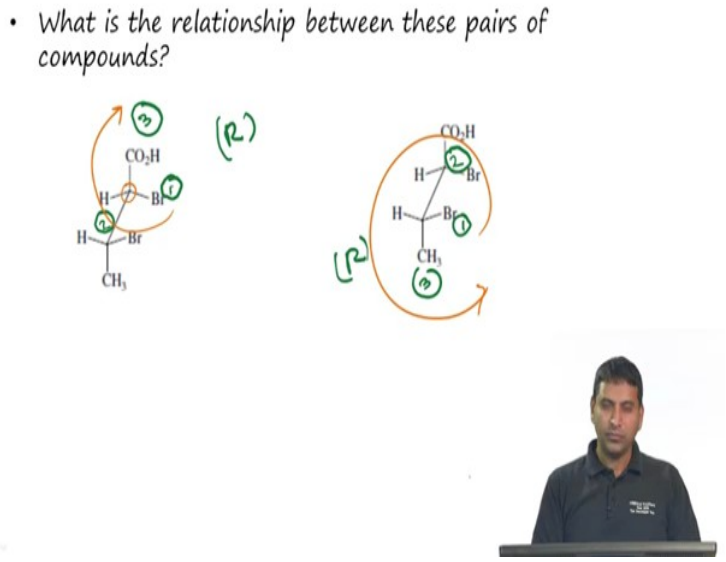

Next question is what is a relationship between these pairs of compounds? So most of you are familiar with the Newman and sawhorse projections. So this is the example of sawhorse projection so we numbered the carbons in the following way 1, 2, 3 and 4 so now in order to address this question first let look at the first molecule and if you see the carbon number 1 over here, the priorities are as shown here 1, 2, 3 and so this would be clockwise and therefore it would be R and if we take these other carbon if you assign the priorities Br is 1, the second carbon is 2 and this methyl is 3 and so you have anticlockwise but since hydrogen is in the opposite side we would call this as R, ok.

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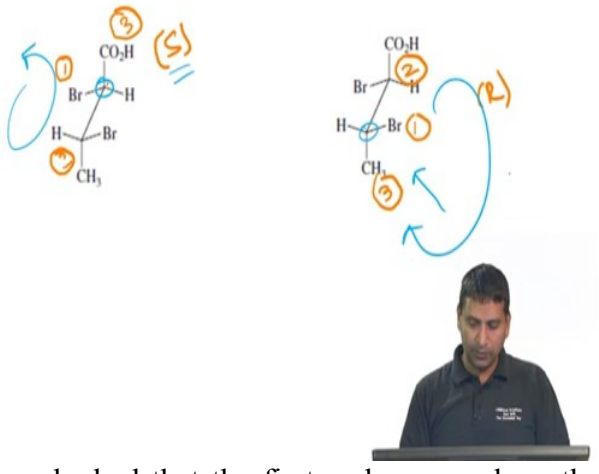

In the second example, we have looked that the first carbon over here the stereochemistry over here would be we need to be determine so in order to determine this will look through

the thing the priorities first is 1, 2, 3 and so now we can look at it from a one angle and it looks so if you look at it from the opposite side of the hydrogen then you have 1, 2, 3 this is anticlockwise and so it would be S, and similarly if you look at the other carbon over here this the absolute stereochemistry is 1, 2 and 3 and so look at it from here then the priority would be 1, 2 and 3 so this would be clockwise and so it would be R.

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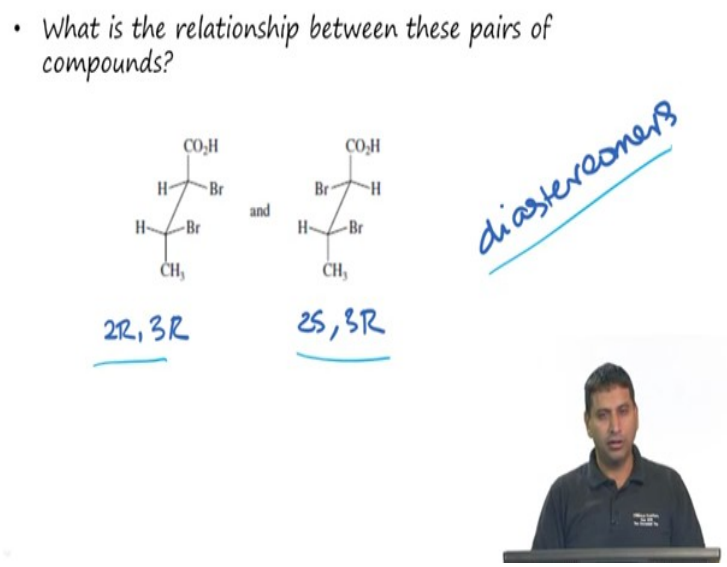

So to look at the stereochemistry we have 2R and 3R where as in the other case 2S and 3R and so these are diastereomers, ok. So some of these questions you will have to practise on your own to get better at it but we should able to assign the absolute stereochemistry with comfort and only then we will be able to determine whether they are identical or diastereomers.

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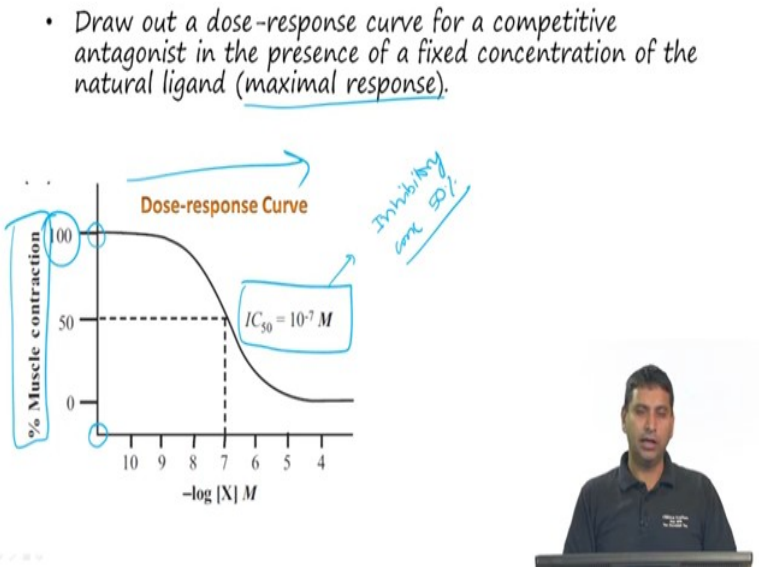

Next question is draw out a dose response curve for a competitive antagonist in the presence of a fixed concentration of the natural ligand and here the fixed concentration of the natural ligand will give us elicit maximal response, ok. So here is a dose response curve that you would see for a competitive antagonist so you see the % Muscle contraction at a very high ligand concentration you will see 100%, so when there is 0 or no competitive antagonist present you do not see any difference in the or you see 100% dose response, as you increase the concentration of the competitive antagonist you will find the dose dependant decrease in the Muscle contraction and so then we can determine what is known as IC_{50} which is basically inhibitory concentration 50% which is the concentration required to inhibit the activity or in this case Muscle contraction by 50%.

So this how the dose response curve for a competitive antagonist in the presence of a fixed concentration of the natural ligand will look like.

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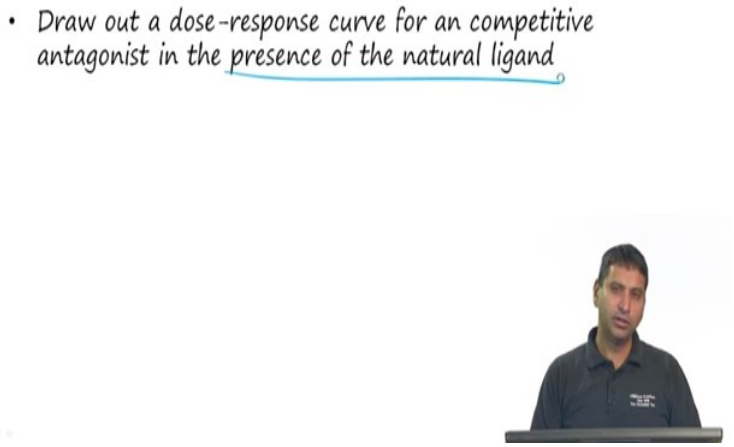

So the next question is draw out a dose response curve for a competitive antagonist in the presence of the natural ligand that means that there is not fixed concentration of the natural ligand but you vary the concentration of the natural ligand and keep the competitive antagonist state of fixed concentration but you can vary it for a particular experiment you will have fixed concentration for the next experiment you will have the higher concentration.

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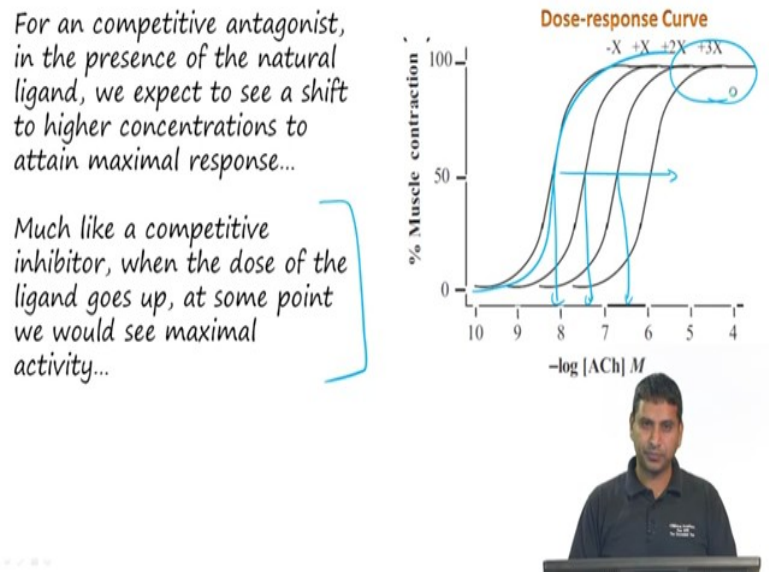

So this is how it looks like again we have seen this in class so in the absence of any antagonist this how the dose response curve would look like and as you add competitive antagonist then the curve moves towards the right which means that the let us say this is the 50% thing it keeps increasing and keeps moving towards the right, ok. So this is much like a competitive inhibitor that we have seen in enzyme inhibition and where the dose of the ligand goes up at some point you will see maximal activity so this is what how a competitive antagonist will look like, in the previous case where we saw in the partial agonist we saw that even if we add keep adding the ligand or the drug you never see a situation where you see a 100% Muscle contraction whereas here if you keep adding large excess of the natural ligand you get complete activity at high doses.

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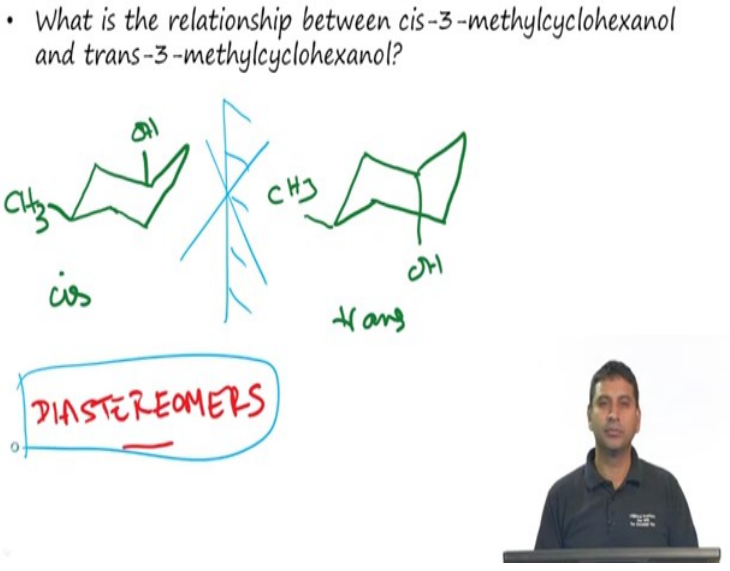

So the next question is what is a relationship between cis-3- methylcyclohexanol and trans-3-methylcyclohexanol? So there are non-super impossible I mean they are not mirror images and so they don't have mirror image relationship but they differ in stereochemistry and therefore they are diastereomers.

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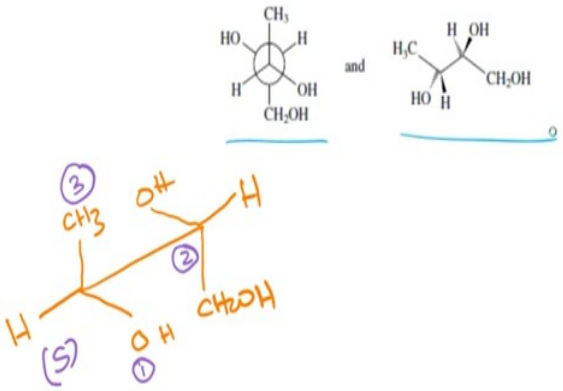

So the next question is what is a relationship between this compound here and this compound here so again I like to follow the systematic method of us doing this so will first assign the stereochemistry of the carbon ahead so that turns out to be S we can go through the process.

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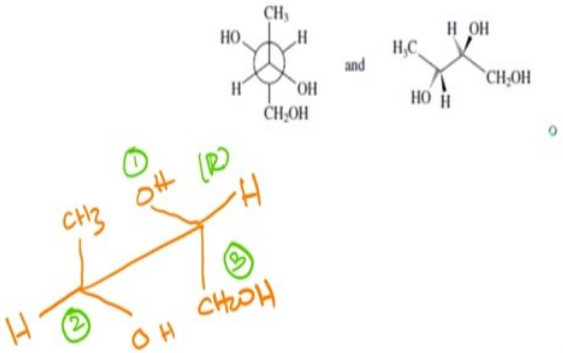

Now we do the same thing for the back carbon and you get the stereochemistry of that to be R, ok and this for the left hand side molecule.

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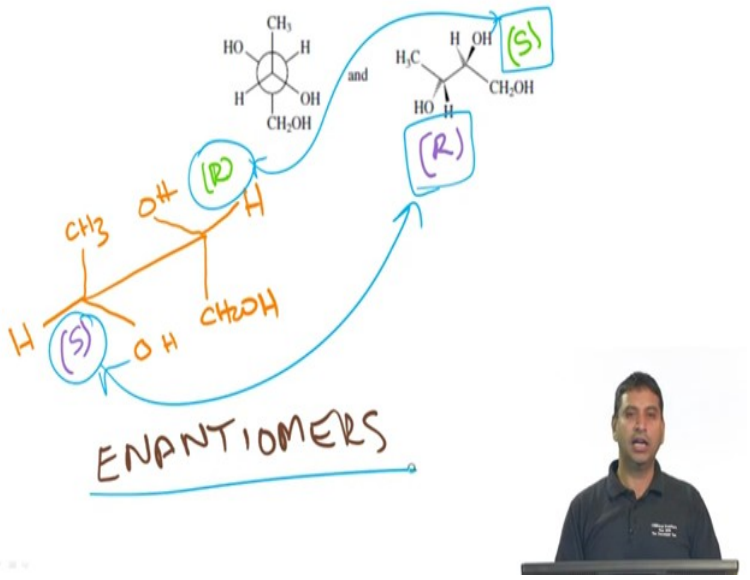

Now for the right hand side molecule we can look at assign the stereochemistry for the front carbon which turns out to be R and the back carbon that turns out to be S, so what we are dealing with here is that these carbon is S which is exactly the opposite and these carbon is R which is exactly the opposite and so we are dealing with enantiomers, ok.

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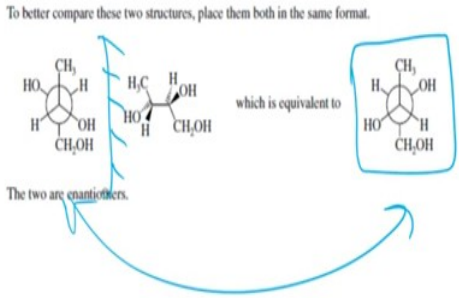

So another way to do this is to write the structure in the Newman projections and compare it so if you see write draw the newman projection for the molecule on the right you get the following conformer and then you can actually draw a mirror plane and you will find that this is these two are exactly mirror images and therefore you can conclude that their enantiomers.

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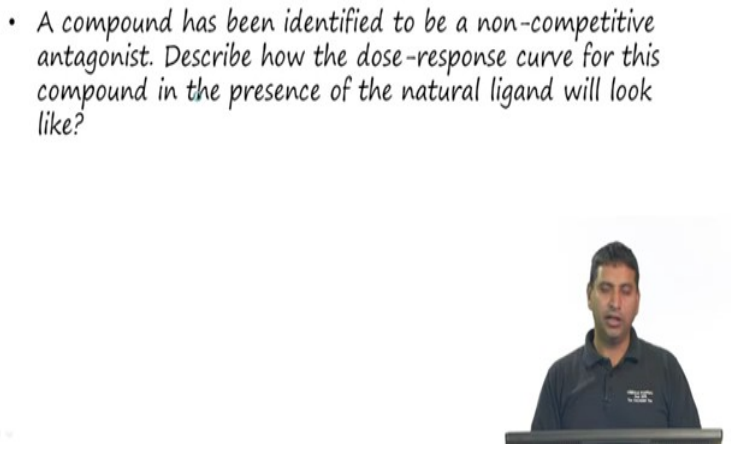

The next question is a compound has been identified to be a non-competitive antagonist, describe how the dose response curve for this compound in the presence of the natural ligand will look like?

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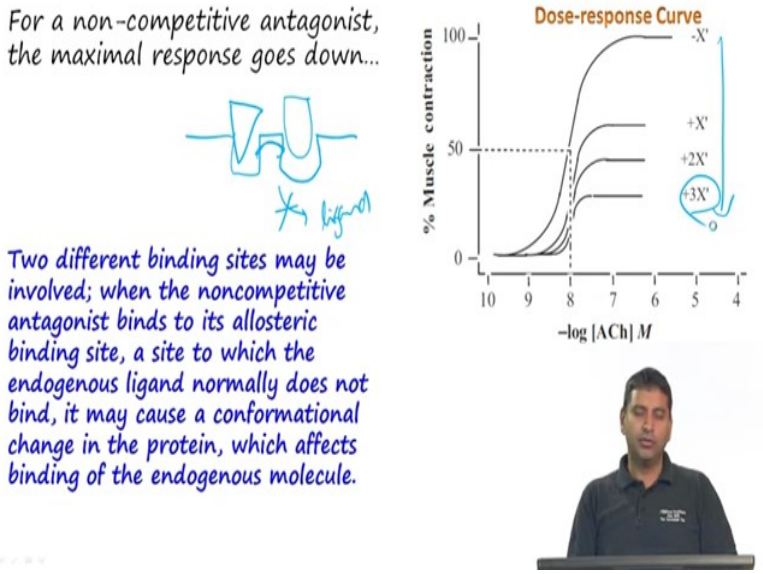

So again we have looked that this in class so far a competitive antagonist you will find that at very high concentrations of the natural ligand you will find that they would be 100% activity, so for a non-competitive antagonist the maximal response will go down ok and this happens as you can see here in this plot the as you increase the dose of the ligand the response goes down, ok.

So this happens because it is possible that there are two different bindings sites may be involved so when the non-competitive antagonist binds to let us say an allosteric binding site

a site to which the endogenous ligand normally does not bind to what may happen is that this might induced a conformational change so let us say your receptor binding to this site over here so this is your receptor binding site where as if your inhibitor binds over here then what it can do is it can induced a conformational change here which will prevent the ligand from binding, ok.

So but this does not happen to a great efficiency and therefore you will find that there is still some activity that is residual activity that happens even if you add if you increase doses of the compounds.

So the way in which we distinguish non-competitive and the competitive is that when the ligand is competing for the same site then when you increase the ligand concentration or even increase the natural ligand concentration at some point it will displace all the drug and it should be able to restore the activity or the activity of the receptors should be 100% or the phenotype that we are looking at here is % Muscle contraction should be 100% but when we looking at a non-competitive situation then since it does not bind to the actual binding site and it does something else which induces a conformational change in the protein which affects the binding of the endogenous molecule what is end up happening is that you will see a reduction in the activity as you increase the dose of the non-competitive inhibitor.